MMHCC
the Mouse Models
of Human Cancers Consortium

MMHCC Newsletter November 2007

MouseLine

The Nobel Assembly at Karolinska Institutet awarded:

The Nobel Prize in Physiology or Medicine 2007 jointly to **Mario R. Capecchi, Martin J. Evans and Oliver Smithies** for their discoveries of **"principles for introducing specific gene modifications in mice by the use of embryonic stem cells"**

This year's Nobel Laureates have made a series of ground-breaking discoveries concerning embryonic stem cells and DNA recombination in mammals. Their discoveries led to the creation of an immensely powerful technology referred to as *gene targeting in mice*. It is now being applied to virtually all areas of biomedicine – from basic research to the development of new therapies.

Gene targeting is often used to inactivate single genes. Such gene "knockout" experiments have elucidated the roles of numerous genes in embryonic development, adult physiology, aging and disease. To date, more than ten thousand mouse genes (approximately half of the genes in the mammalian genome) have been knocked out. Ongoing international efforts will make "knockout mice" for all genes available within the near future.

With gene targeting it is now possible to produce almost any type of DNA modification in the mouse genome, allowing scientists to establish the roles of individual genes in health and disease. Gene targeting has already produced more than five hundred different mouse models of human disorders, including cardiovascular and neuro-degenerative diseases, diabetes and cancer.

The complete press release is attached to the newsletter.

For interviews with the laureates please point your browser to:
http://nobelprize.org/nobel_prizes/medicine/laureates/2007/index.html

Meetings

September 16 - 22, 2004
Short Course on Mathematical Approaches to the Analysis of Complex Phenotypes
Bar Harbor, Maine
Meeting Information: http://www.jax.org/courses/events/coursedetails.do?id=35

November 14 – 17, 2007
AACR-Advances in Colon Cancer Research
Cambridge, Massachusetts
Meeting Information: http://www.aacr.org/home/scientists/meetings--workshops/special-conferences/advances-in-colon-cancer-research.aspx

December 1 – 5, 2007
The 47th Annual Meeting of The American Society for Cell Biology
Washington, D.C.
Meeting Information: http://www.ascb.org/meetings/

December 2 – 7, 2007
Colony Management: Principles and Practices
Bar Harbor, Maine
Meeting Information: http://www.jax.org/courses/2007/colony_fall07.html

December 5 – 8, 2007
AACR-Sixth International Conference on Frontiers in Cancer Prevention Research
Philadelphia, Pennsylvania
Meeting Information: http://www.aacr.org/home/scientists/meetings--workshops/frontiers-in-cancer-prevention-research.aspx

December 6 – 9, 2007
AACR-The Role of Telomeres and Telomerase in Cancer Research
San Francisco, California
Meeting Information: http://www.aacr.org/home/scientists/meetings--workshops/special-conferences/the-role-of-telomeres-and-telomerase-in-cancer-research.aspx

December 8 - 11, 2007
American Society for Hematology (ASH): 49th Annual Meeting and Exposition
Atlanta, Georgia
Meeting Information: http://www.hematology.org/meetings/2007/index.cfm

Notices and Funding Opportunities

NIH Announces Plans to Eliminate Paper Notification of Notice of Award (NoA) Letters
NOT-OD-08-002
National Institutes of Health
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-002.html

Implementation of the Revised American Veterinary Medical Association Guidelines on Euthanasia
NOT-OD-08-005
Office of the Director, NIH
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-005.html

New Features in eRA Commons
NOT-OD-08-007
National Institutes of Health
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-007.html

Network for Translational Research (NTR): Optical Imaging in Multimodal Platforms (U54)
RFA-CA-08-002
National Cancer Institute
http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-002.html

Bioinformatics

caMOD 2.3 released
Version 2.3 of the Cancer Models Database (caMOD) was release on October 30th, 2007.

With this version, caMOD starts customizing the application for models in a variety of species beyond mouse models. caMOD 2.3 supports the submission of zebrafish and rat models. Depending on the selected species, the application uses species-specific vocabularies for anatomy and disease on the Histopatholoy, Cell Lines, Graft, and Associated Expression pages. Links to the Zebrafish Model Organism Database (http://www.zfin.org) and to the Rat Genome Database (http://rgd.mcw.edu/) are provided on the Genetic Description pages and allow the user to retrieve information about the modified alleles. Links to the above mentioned resources have also been added to the publication listings.
Data about other species can be submitted to caMOD, but no vocabularies for anatomical or diagnostic terms are provided at this time.
The Search pages now utilize the species-specific vocabularies. The selection drop down list of model species on the Search pages is created dynamically depending on which models have been approved during the review process.

caMOD 2.3 further expands the use of vocabularies provided by NCI Thesaurus (http://nciterms.nci.nih.gov) by introducing the staining method vocabulary to the Image portion of the application.

Acknowledgements
The rat vocabularies were retrieved from RENI. We would like to thank the members of the Rat Nomenclature Reconciliation Subcommittee for their support and advice.
The zebrafish vocabularies were provided by ZFIN, the Zebrafish Model Organism Database, and rendered from bioontology.org.

RENI: http://www.item.fraunhofer.de/reni/rat_nomenclature/index.htm
ZFIN: http://www.zfin.org
Bioontology: http://www.bioontology.org

Our special thank you goes to Dr. Hatem Sabaawy who served as the domain expert on zebrafish models. We would also like to thank the NCI CBIIT Enterprise Vocabulary Systems team for their work in converting and importing the vocabularies.

Internship @ CBIIT

Department of Health and Human Services (DHHS)
National Institutes of Health (NIH)
National Cancer Institute (NCI)
Center for Biomedical Informatics
And
Information Technology (CBIIT)

INTERN FOR ANIMAL MODEL AND MICROARRAY DATA CURATION

The Center for Biomedical Informatics and Information Technology (CBIIT), located in Rockville, MD, provides professional, industrial quality software development and data management services to the clinical and basic science research communities. Our partners include national leaders in all areas of cancer research, including cancer genomics, proteomics, early detection, therapy evaluation and prevention. Our contractors and staff include senior scientists, bioinfomaticians, as well as professional software architects and engineers.

The CBIIT is recruiting for an intern to extract animal model data from primary scientific literature and enter this data into the Center's Cancer Model Database (caMOD). Additionally, this intern will enter microarray data associated with these models into the Center's microarray database (caArray). These efforts will require follow up with the laboratory personnel who generated the data and thus good communication skills and addition to detail are required.

The duration of the internship is one year and will be awarded through NCI's Cancer Research Training Award (CRTA) Program. The successful candidate will have a Bachelor's degree in biomedical sciences and one year of laboratory research experience. Basic knowledge of computers and databases is required. Experience working with animal models is an advantage. Work will be performed in the CBIIT Rockville office.

More information about CBIIT is available at http://ncicb.nci.nih.gov.
Applicants should send their resume to the Juli Klemm, Ph.D. (klemmj@mail.nih.gov).

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Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

Karolinska Institutet

PRESS RELEASE 2007-10-08

The Nobel Assembly at Karolinska Institutet has today decided to award

The Nobel Prize in Physiology or Medicine 2007

jointly to

Mario R. Capecchi, Martin J. Evans and Oliver Smithies

for their discoveries of

"principles for introducing specific gene modifications in mice by the use of embryonic stem cells"

SUMMARY

This year's Nobel Laureates have made a series of ground-breaking discoveries concerning embryonic stem cells and DNA recombination in mammals. Their discoveries led to the creation of an immensely powerful technology referred to as *gene targeting in mice*. It is now being applied to virtually all areas of biomedicine – from basic research to the development of new therapies.

Gene targeting is often used to inactivate single genes. Such gene "knockout" experiments have elucidated the roles of numerous genes in embryonic development, adult physiology, aging and disease. To date, more than ten thousand mouse genes (approximately half of the genes in the mammalian genome) have been knocked out. Ongoing international efforts will make "knockout mice" for all genes available within the near future.

With gene targeting it is now possible to produce almost any type of DNA modification in the mouse genome, allowing scientists to establish the roles of individual genes in health and disease. Gene targeting has already produced more than five hundred different mouse models of human disorders, including cardiovascular and neuro-degenerative diseases, diabetes and cancer.

Modification of genes by homologous recombination

Information about the development and function of our bodies throughout life is carried within the DNA. Our DNA is packaged in chromosomes, which occur in pairs – one inherited from the father and one from the mother. Exchange of DNA sequences within such chromosome pairs increases genetic variation in the population and occurs by a process called *homologous recombination.* This process is conserved throughout evolution and was demonstrated in bacteria more than 50 years ago by the 1958 Nobel Laureate Joshua Lederberg.

Mario Capecchi and Oliver Smithies both had the vision that homologous recombination could be used to specifically modify genes in mammalian cells and they worked consistently towards this goal.

Capecchi demonstrated that homologous recombination could take place between introduced DNA and the chromosomes in mammalian cells. He showed that defective genes could be repaired by homologous recombination with the incoming DNA. Smithies initially tried to repair mutated genes in human cells. He thought that certain inherited blood diseases could be treated by correcting the disease-causing mutations in bone marrow stem cells. In these attempts Smithies discovered that endogenous genes could be targeted irrespective of their activity. This suggested that all genes may be accessible to modification by homologous recombination.

Embryonic stem cells – vehicles to the mouse germ line

The cell types initially studied by Capecchi and Smithies could not be used to create gene-targeted animals. This required another type of cell, one which could give rise to germ cells. Only then could the DNA modifications be inherited.

Martin Evans had worked with mouse embryonal carcinoma (EC) cells, which although they came from tumors could give rise to almost any cell type. He had the vision to use EC cells as vehicles to introduce genetic material into the mouse germ line. His attempts were initially unsuccessful because EC cells carried abnormal chromosomes and could not therefore contribute to germ cell formation. Looking for alternatives Evans discovered that chromosomally normal cell cultures could be established directly from early mouse embryos. These cells are now referred to as *embryonic stem (ES) cells*.

The next step was to show that ES cells could contribute to the germ line (see Figure). Embryos from one mouse strain were injected with ES cells from another mouse strain. These *mosaic* embryos (i.e. composed of cells from both strains) were then carried to term by surrogate mothers. The mosaic offspring was subsequently mated, and the presence of ES cell-derived genes detected in the pups. These genes would now be inherited according to Mendel’s laws.

Evans now began to modify the ES cells genetically and for this purpose chose retroviruses, which integrate their genes into the chromosomes. He demonstrated transfer of such retroviral DNA from ES cells, through mosaic mice, into the mouse germ line. Evans had used the ES cells to generate mice that carried new genetic material.

Two ideas come together – homologous recombination in ES cells

By 1986 all the pieces were at hand to begin generating the first gene targeted ES cells. Capecchi and Smithies had demonstrated that genes could be targeted by homologous recombination in cultured cells, and Evans had contributed the necessary vehicle to the mouse germ line – the ES-cells. The next step was to combine the two.

For their initial experiments both Smithies and Capecchi chose a gene (hprt) that was easily identified. This gene is involved in a rare inherited human disease (Lesch-Nyhan syndrome). Capecchi refined the strategies for targeting genes and developed a new method (positive-negative selection, see Figure) that could be generally applied.

Birth of the knockout mouse – the beginning of a new era in genetics

The first reports in which homologous recombination in ES cells was used to generate gene-targeted mice were published in 1989. Since then, the number of reported knockout mouse strains has risen exponentially. Gene targeting has developed into a highly versatile technology. It is now possible to introduce mutations that can be activated at specific time points, or in specific cells or organs, both during development and in the adult animal.

Gene targeting is used to study health and disease

Almost every aspect of mammalian physiology can be studied by gene targeting. We have consequently witnessed an explosion of research activities applying the technology. Gene targeting has now been used by so many research groups and in so many contexts that it is impossible to make a brief summary of the results. Some of the later contributions of this year's Nobel Laureates are presented below.

Gene targeting has helped us understand the roles of many hundreds of genes in mammalian fetal development. Capecchi's research has uncovered the roles of genes involved in mammalian organ development and in the establishment of the body plan. His work has shed light on the causes of several human inborn malformations.

Evans applied gene targeting to develop mouse models for human diseases. He developed several models for the inherited human disease cystic fibrosis and has used these models to study disease mechanisms and to test the effects of gene therapy.

Smithies also used gene targeting to develop mouse models for inherited diseases such as cystic fibrosis and the blood disease thalassemia. He has also developed numerous mouse models for common human diseases such as hypertension and atherosclerosis.

In summary, gene targeting in mice has pervaded all fields of biomedicine. Its impact on the understanding of gene function and its benefits to mankind will continue to increase over many years to come.

Mario R. Capecchi, born 1937 in Italy, US citizen, PhD in Biophysics 1967, Harvard University, Cambridge, MA, USA. Howard Hughes Medical Institute Investigator and Distinguished Professor of Human Genetics and Biology at the University of Utah, Salt Lake City, UT, USA.

Sir Martin J. Evans, born 1941 in Great Britain, British citizen, PhD in Anatomy and Embryology 1969, University College, London, UK. Director of the School of Biosciences and Professor of Mammalian Genetics, Cardiff University, UK.

Oliver Smithies, born 1925 in Great Britain, US citizen, PhD in Biochemistry 1951, Oxford University, UK. Excellence Professor of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, NC, USA.

General strategy for gene targeting in mice